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| 09/202,464 | 03/09/1999 | KOHSUKE KINO | 06501/024001 | 2927 |

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| ART UNIT | PAPER NUMBER |
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| 1644 | 19 |

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/202,464 | Applicant(s) KINO ET AL. | |
|---|---|---|---|
| | Examiner " Neon" Phuong Huynh | Art Unit 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,5,7,11,13,14,17 and 20-39* is/are pending in the application.

4a) Of the above claim(s) *2,7,11,13,14,17,20-28,36 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,32,38 and 39* is/are rejected.

7)☐ Claim(s) *29-31, and 33-35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. Claims 1-2, 5, 7, 11, 13-14, 17, 20-39 are pending.

2. Claims 2, 7, 11, 13-14, 17, 20-28 and 36-37 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In response to Applicant's traverse of the Restriction requirement in Office Action mailed 12/4/01, Applicant's election with traverse of Group I, Claims 1, 3 and 5, drawn to Cha o1 peptides that read on species peptide #1-22 (now SEQ ID NO: 24), is acknowledged. The traversal is on the grounds that (1) this application was filed under § 371 and entitled to "unity of invention" and not to the US rules of restriction practice; (2) the lack of a special technical feature that defines the contribution of the instant invention over Ikagawa et al cannot rendered obvious because Ikagawa et al discloses peptides and analog thereof from Cry 1 j, which is a polypeptide of Japanese cedar pollen whereas the peptides of instant application is derived from Cha o1 and Cha o 2 which are polypeptides of Japanese cypress pollen. However, WO 94/01560 publication (Jan 1994, PTO 1449) teaches a peptide such as CJI-26, comprising at least one T-cell epitope of pollen allergen consisting of an amino acid sequence which is identical to the claimed peptide #1-26 (SEQ ID NO: 28) of instant application (See Fig 13 of WO94/01560, in particular) at the time the election was made. Since Applicants' inventions do not contribute a special technical feature when viewed over the prior art, they do not have a single general inventive concept and therefore lack unity of invention under § 371. The requirement is still deemed proper and is therefore made FINAL.

4. In response to species election, applicant has elected peptide #1-22 (SEQ ID NO: 24) filed 9/24/01 is acknowledged. In response to Office Action mailed 12/4/01, Applicants have subsequently removed peptide #1-26 (SEQ ID NO: 28) from claim 1 to overcome the rejection under 35 USC 102(b). In light of the removal of peptide SEQ ID NO: 28 to obviate anticipation by the WO 94/01560 reference, the prior art search has been extended to include peptides consisting of an amino acid sequence selected from the group consisting of SEQ ID NOS: 4, 6-10, 12-14, 16-18, 21-27, 29, and 32-36.

5. In response to rejoinder of Inventions of Groups III (claim 7) which drawn to a method of treating or preventing pollinosis, Group V (claim 17) drawn to a method of diagnosing pollinosis, Group VI (claims 18-19) drawn to analog of Japanese cypress pollen allergen Cha o1, Group VII (claim 20) drawn to a process of making analog of Japanese cypress pollen allergen Cha o1, and Group XI (claims 25-26) drawn to a modified peptide of Japanese cypress pollen allergen Cha o1 using invention of Group I which drawn to a composition comprising at least two T-cell epitopes of Japanese cypress pollen allergen Cha o1, only claims directed to the process of making or using the patentable product, previously withdrawn from consideration as a result of a restriction requirement, will be rejoined in Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86). Until the patentable product is allowed, Claims 2, 7, 11, 13-14, 17, 20-28 and 36-37 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

6. The following new grounds of objection and rejections are necessitated by the amendment filed 5/21/02.

7. Claims 29-31 are objected to under 37 CFR 1.821(d) because SEQ ID NO is required.

8. Claims 5, and 33-35 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

Claims 5 and 33-35 as written represent a departure from the specification and the claims as originally filed. The recitation of "consisting essentially of" has no support in the specification as filed. Applicant has not point out the support for said "consisting essentially of".

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 5, 32, 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a peptide consisting of at least one T-cell epitope of

Japanese cypress pollen Cha o1, and optionally a linker sensitive to enzyme cleavage between two epitopes, wherein each of said epitopes consisting of an amino acid sequence selected from the group consisting of SEQ ID NOS: 4, 6-10, 12-14, 16-18, 21-27, 29, and 32-36 shown in Fig 4, (2) a composition consisting of the peptide mentioned above a an active ingredient and a pharmaceutically acceptable diluent or carrier, (3) the composition mentioned above for treating pollinosis wherein the pollinosis is Japanese cypress pollinosis and/or cedar pollinosis, **does not** reasonably provide enablement for (1) *any* peptide consisting of *any* part of a T-cell epitope of Japanese cypress pollen Cha o1, and optionally a linker sensitive to enzyme cleavage between two epitopes, wherein each of said epitopes consisting of an amino acid sequence selected from the group consisting of SEQ ID NOS: 4, 6-10, 12-14, 16-18, 21-27, 29, and 32-36 shown in Fig 4 for peptide base immunotherapy, (2) a composition consisting essentially of *any* peptide consisting of *any* part of a T-cell epitope of Japanese cypress pollen Cha o1, and optionally a linker sensitive to enzyme cleavage between two epitopes, wherein each of said epitopes consisting of an amino acid sequence selected from the group consisting of SEQ ID NOS: 4, 6-10, 12-14, 16-18, 21-27, 29, and 32-36 shown in Fig 4 for pollinosis wherein the pollinosis is Japanese cypress pollinosis and/or cedar pollinosis, (3) the peptide mentioned above wherein the linker is Arg-Arg or Lys-Lys, and (4) a peptide consisting of any part of an amino acid sequence of at least two T-cell epitopes of Japanese cypress pollen allergen Cha o1 and a linker sensitive to enzyme cleavage between two T-cell epitopes wherein each of said epitopes consisting of an amino acid sequence selected from the group consisting of SEQ ID NOS: 4, 6-10, 12-14, 16-18, 21-27, 29, and 32-36 shown in Fig 4 for preventing pollinosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only (1) a peptide consisting of at least one or two T-cell epitopes of Japanese cypress pollen allergen Cha o 1 consisting of amino acid sequence selected from the group consisting of peptide of SEQ ID NOS: 4, 6-10, 12-14, 16-18, 21-29, 32-36 shown in Fig 4, (2) a composition comprising said peptide and an acceptable diluent or carrier for in vitro diagnosis of pollinosis and peptide-based immunotherapy.

The specification does not teach how to make and use *any* part of amino acid sequence of at least one T-cell epitope or two T-cell epitopes of Japanese cypress pollen Cha o1 such as the ones recited in claim 1 that would even bind to a T cell receptor or mediate an interaction with a major histocompatibility complex (MHC) class II molecule, in turn, would stimulates T cell to produce interferon gamma for preventing pollinosis. There is a lack of guidance and working example with respect to the specific amino acid residues within any part of amino acid sequence mentioned above that can be added, substituted deleted and modified such that after modification the resulting peptide would bind to T cell receptor, in turn, stimulate T cell to produce interferon gamma for treating pollinosis. The term "part of said amino acid sequence" is vague; the "part" could be as little as one amino acid. It is not clear how "a part of an amino acid sequence" such as one or two amino acids of any peptide mentioned above could still bind to the MHC class II receptor.

Berzofsky *et al* (in Fundamental Immunology 2nd edition) teach the size of a peptide that binds to the peptide binding cleft of class II MHC expressing T cell is at least 10 to 20 amino acids long; T cell response to peptide such as pigeon cytochrome c depends on Class II molecule on the APCs and even a single amino acid substitution such as Lys at position 99 on the peptide destroyed the ability to stimulate T cell clones specific for the peptide while Ala substitution or deletion at position 103 stimulate T cell proliferation (See page 196, column 1, last paragraph, in particular).

Hoyne *et al* teach the success of peptide based immunotherapy depends on the decrease of T cell response such as a decrease in Th2 type cytokine production by allergen specific Th cells or allergen derived peptide that are recognized by specific CD4+ T cells. There are a number of problems that need to be addressed before peptides can make the transition from experimental systems to clinical application such as peptides containing immunodominant epitopes are more potent tolergens than those containing minor epitopes. In order to obtain information on the distribution of immunodominant T cell epitopes for a particular allergen, it will be necessary to perform **detailed epitope analysis** on the peripheral repertoire of a large

panel of allergic patients of known HLA haplotypes (See page 184, second paragraph, in particular). Since recognition of peptide epitopes by T cells is dependent on the presentation of peptide by appropriate MHC molecule and for maximum efficacy, the peptide should be short and selected on the basis of their ability to bind to MHC molecules.

There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. Fasler *et al.* teach that peptides derived from house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al.* further teach that substituting a neutral Asn residue at position 173 with a basic Lysine, a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine also did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular). Burks *et al.* teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Stanley *et al* teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley et al also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Given the indefinite number of undisclosed peptide, it is unpredictable which undisclosed part of any amino acid sequence of T-cell epitope of Japanese cypress pollen allergen Cha o 1 mentioned above would be useful for any purpose. Since the specification fails to provide guidance regarding which part of the or which amino acid within the peptide can tolerate change, it follows that a

composition consisting essentially of *any* peptide consisting of *any* part of a T-cell epitope of Japanese cypress pollen Cha o1 mentioned above is not enable. Further, there is no in vivo working example that any peptide mentioned could prevent or avert pollinosis caused by cedar or Japanese cypress or cedar pollen. Since the peptide consisting of *any* part of a T-cell epitope of Japanese cypress pollen Cha o1 is not enabled, it follows that the linker Arg-Arg or Lys-Lys linking between two T-cell epitopes is not enabled.

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

11. Claims 1, 5, 32, 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* peptide consisting of *any* part of a T-cell epitope of Japanese cypress pollen Cha o1, and optionally a linker sensitive to enzyme cleavage between two epitopes, wherein each of said epitopes consisting of an amino acid sequence selected from the group consisting of SEQ ID NOS: 4, 6-10, 12-14, 16-18, 21-27, 29, and 32-36 shown in Fig 4 for peptide base immunotherapy, (2) a composition consisting essentially of *any* peptide consisting of *any* part of a T-cell epitope of Japanese cypress pollen Cha o1, and optionally a linker sensitive to enzyme cleavage between two epitopes, wherein each of said epitopes consisting of an amino acid sequence selected from the group consisting of SEQ ID NOS: 4, 6-10, 12-14, 16-18, 21-27, 29, and 32-36 shown in Fig 4 for pollinosis wherein the pollinosis is Japanese cypress pollinosis and/or cedar pollinosis, (3) the peptide mentioned above wherein the linker is Arg-Arg or Lys-Lys, and (4) a peptide consisting of any part of an amino acid sequence of at least two T-cell epitopes of Japanese cypress pollen allergen Cha o1 and a linker sensitive to enzyme cleavage between two T-cell epitopes wherein each of said epitopes consisting of an amino acid sequence selected from the group consisting of

SEQ ID NOS: 4, 6-10, 12-14, 16-18, 21-27, 29, and 32-36 shown in Fig 4 for preventing pollinosis.

The specification discloses only (1) a peptide consisting of at least one or two T-cell epitopes of Japanese cypress pollen allergen Cha o 1 and consisting of amino acid sequence selected from the group consisting of peptide of SEQ ID NOS: 4, 6-10, 12-14, 16-18, 21-29, 32-36 shown in Fig 4, (2) a composition comprising said peptide and an acceptable diluent or carrier for in vitro diagnosis of pollinosis and peptide-based immunotherapy.

There is insufficient written description about the structure associated with function of *any* peptide consisting of *any* part of a T-cell epitope of Japanese cypress pollen Cha o1 and any composition consisting essentially of said peptide consisting of *any* part of a T-cell epitope of Japanese cypress pollen Cha o1 mentioned above for preventing pollinosis. The term "part of said amino acid sequence" is vague; the "part" could be as little as one amino acid. It is not clear how "a part of an amino acid sequence" such as one or two amino acids of any peptide mentioned above could even bind to the MHC class II receptor, in turn, stimulates interferon gamma production for treating or preventing pollinosis. Given the lack of a written description of any additional peptide consisting of *any* part of a T-cell epitope of Japanese cypress pollen Cha o1 and a method of "preventing" pollinosis, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "said pollinosis" in claim 32 has no antecedent basis in base claim 5. Base claim 5 requires a composition consisting essentially of the peptide of claim 1, as an active ingredient, and a pharmaceutically acceptable diluent or carrier.

14. Claims 29-31, and 33-35 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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August 12, 2002

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